Journal of the American College of Cardiology
Vol. 49, No. 2, 2007

ISSN 0735-1097/07/$32.00

CORRESPONDENCE

Research Correspondence

α_{2c}Del322-325 and β_1Arg389 Adrenergic Polymorphisms Are Not Associated With Reduced Left Ventricular Ejection Fraction or Increased Left Ventricular Volume

To the Editor: Polymorphisms in adrenergic receptors are potential risk factors for developing systolic heart failure (HF) presumably via modulation of sympathetic nervous system activity (1). Two such polymorphisms (α_{2c}Del322-325 and β_1Arg389) appear to have adverse synergistic effects, with the α_{2c}Del322-325 receptor increasing synaptic norepinephrine levels via loss of negative feedback and the β_1Arg389 receptor increasing responsiveness to norepinephrine. In a prior study, others demonstrated that African Americans with both of these polymorphisms were at increased risk of HF (1). If this association was robust, we reasoned that these 2 polymorphisms would also be strongly associated with phenotypes that are precursors to systolic HF such as increased left ventricular end-diastolic volume (EDV) and decreased left ventricular ejection fraction (LVEF). The Dallas Heart Study (DHS), a large multiethnic population-based probability sample of Dallas County, afforded the opportunity to test this hypothesis.

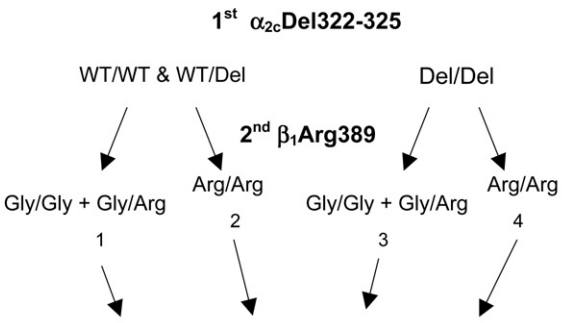
The design of the DHS, conducted at 3 sequential visits, has been described including sampling methods and validation (2), assignment of race, and its cardiac magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry protocols (3,4). To determine whether subjects had a history of HF, participants were first asked: "Has a doctor or other health professional ever told you that you had any kind of heart problems or a heart condition?" If they answered "Yes," they were subsequently asked: "Has a doctor or other health professional ever told you that you have congestive HF, an enlarged heart, a weak heart, or cardiomyopathy?" Subjects who answered yes to both questions were classified as having a history of HF. A reduced LVEF was defined as <61% in women and <55% in men as recently reported (4). Gentoypes for β_1Arg389 were ascertained using allelic discrimination (Applied Biosystems, Foster City, California) and for α_{2c}Del322-325 by a size fractionation assay. For the latter, we amplified the *ADRA2C* gene from genomic DNA using oligonucleotides 5′-FAM-GTCTACGCGCGCATCTACCGAGTGGCCAAG-3′ + antisense primer 5′-CCCATGACCACAGCCAGCACAAAGGTG AAG-3′. Amplicons were size-fractionated on an ABI 3100-automated DNA sequencer. Informed consent was obtained, and the Institutional Review Board of University of Texas Southwestern Medical Center approved this protocol.

We restricted our analyses to participants who were white or black, had available genotype data at the 2 loci of interest, and underwent cardiac MRI (n = 1,861). We classified subjects into 1 of 4 mutually exclusive categories (1): group 1: heterozygote or wild-type at both loci; group 2: heterozygote or wild-type at α_{2c}Del322-325 and homozygote at β_1Arg389; group 3: homozygote at α_{2c}Del322-325 and heterozygote or wild-type at β_1Arg389; and group 4: homozygote at both loci. Data were analyzed using the SAS (version 9.1, SAS Corp., Cary, North Carolina) statistical software package. Continuous variables are presented as mean ± SD. Associations between genotype and categorical variables were tested using Fisher exact test. Group differences in means of B-type natriuretic peptide were tested using the non-parametric Kruskal-Wallis test. Group differences in means of other continuous variables were tested using the 1-way analysis of variance F-test of the group effect. Post hoc we calculated the power to detect a 4-point LVEF difference and a 5 ml/m^2 difference in EDV/body surface area (BSA) between groups 1 and 4 (see the preceding text). For all analyses, 2-tailed p values <0.05 were considered statistically significant.

Our study cohort included 1,121 African-American and 740 white subjects (58% and 51% women, respectively) with a mean age of 45 ± 10 years. The allele frequency of α_{2c}Del322-325 was 0.40 in African Americans and 0.06 in whites, yielding 17% and 0.8% homozygous, respectively. The allele frequency of β_1Arg389 was 0.58 in African-American and 0.72 in white subjects, yielding 35% and 52% homozygous, respectively. In African Americans, the prevalence of diabetes was 13%, hypertension 42%, and obesity (body mass index ≥30 kg/m^2) 51%.

When African-American subjects were classified into 1 of 4 groups (1), we found no association between genotype group with either B-type natriuretic peptide levels, self-reported history of HF, or measures of left ventricular structure and function (Fig. 1). When these analyses were repeated in white subjects, recognizing the lower allele frequency of α_{2c}Del322-325, there again was no association of genotype group and cardiac traits (data not shown). In African Americans, the power to detect a 4-point decrease in LVEF in group 4 versus group 1 (from 74% to 70%) was 94%, and the power to detect a 5-point increase in EDV/BSA between these 2 groups (from 51 to 56 ml/m^2) was 81%.

In this study, we attempted to replicate the putative association of α_{2c}Del322-325 and β_1Arg389 with increased risk of systolic HF in African-American subjects (1). Although studies of white Italian (5) and Japanese patients (6) have demonstrated no association of these polymorphisms and risk of HF, to our knowledge no replication in African-American patients has been conducted. We found very similar allele frequencies of α_{2c}Del322-325 and β_1Arg389 as previously reported (1). However, we were unable to demonstrate an association of these 2 alleles with reduced LVEF or increased ventricular volume, traits that are considered precursors to systolic HF. Further, there was no association of genotype with levels of B-type natriuretic peptide or self-reported history of



	1 (N = 615)	2 (N = 321)	3 (N = 115)	4 (N = 70)	P-value
Male gender	42%	42%	43%	42%	1
BNP pg/ml	17 ± 55	11 ± 24	25 ± 105	10 ± 21	0.14
CHF (%)	4	5	8	3	0.3
LVEF (%)	71 ± 9	72 ± 8	72 ± 9	72 ± 8	0.7
Reduced LVEF† (%)	6	4	4	4	0.6
LV mass / FFM (g/kg)	3.1 ± 0.7	3.0 ± 0.5	3.1 ± 0.6	3.1 ± 0.6	0.12
End-diastolic volume/BSA (ml/m2)	52 ± 14	51 ± 11	55 ± 16	52 ± 12	0.06
End-systolic volume/BSA (ml/m2)	16 ± 10	14 ± 6	16 ± 14	14 ± 5	0.14

Figure 1 **Association of Genotype Combinations With BNP Levels, History of Heart Failure, and LV Structure and Function in African Americans**

Classification is based on Small et al. (1). The classification first stratifies subjects by whether they are homozygote for the α_{2c}Del322-325 polymorphism, and then second by whether they are homozygote for the β_1Arg389 polymorphism. α_{2c}Del322-325 genotypes are classified as WT/WT: homozygous wild-type; WT/Del: heterozygote; Del/Del: homozygous for α_{2c}Del322-325. †Reduced left ventricular ejection fraction (LVEF) defined as <61% for females and <55% for males (4). BNP = B-type natriuretic peptide; BSA = body surface area; CHF = self-reported heart failure; FFM = fat-free mass. Data are presented as mean ± SD or as %.

HF. In total, these data question the strength of the association of these alleles and risk of developing systolic HF.

The main limitation of our study is that the DHS is a healthier population-based cohort as compared with the original study cohort comprised of patients with symptomatic HF (1). Nevertheless, we had 94% power to detect an association of the polymorphisms with a 4-point decrement in LVEF and 81% power to detect an increase in EDV/BSA of 5 ml/m^2. Other polymorphisms in α_{2c}-adrenergic receptor have been shown to influence its expression, thereby potentially modulating the cardiomyopathic properties of α_{2c}Del322-325 (7). Although we did not genotype our subjects for these additional polymorphisms and thus cannot perform a haplotype-based analysis, it nevertheless was important to test the strength of the previously reported association of α_{2c}Del322-325 and β_1Arg389 with risk of HF in African-Americans subjects.

In a large population cohort of African-American subjects, we found there was no association between the combination of α_{2c}Del322-325 and β_1Arg389 and traits commonly accepted to be precursors of systolic HF.

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doi:10.1016/j.jacc.2006.10.016

Please note: The Dallas Heart Study is funded by a center grant from the Donald W. Reynolds Foundation. Dr. Mark Drazner was the recipient of a Clinical Scientist Development Award and Anne Chung was the recipient of a Doris Duke Research Fellow grant, both from the Doris Duke Charitable Foundation (New York, New York). Dr. Auchus has reported that he is on a speakers' bureau for Pfizer, Inc. and Columbia Laboratories and a consultant for Cougar Biotechnology.

REFERENCES

1. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB. Synergistic polymorphisms of β_1- and α_{2c}-adrenergic receptors and the risk of congestive heart failure. N Engl J Med 2002;347:1135–42.
2. Victor RG, Haley RW, Willett DL, et al. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. Am J Cardiol 2004; 93:1473–80.

3. Drazner MH, Dries DL, Peshock RM, et al. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. Hypertension 2005;46:124–9.
4. Chung AK, Das SR, Leonard D, et al. Women have a higher left ventricular ejection fraction than men independent of their differences in left ventricular volume. Circulation 2006;113:1597–604.
5. Metra M, Zani C, Covolo L, et al. Role of β_1- and α_{2c}-adrenergic receptor polymorphisms and their combination in heart failure: a case-control study. Eur J Heart Fail 2006:8:131–5.
6. Nonen S, Okamoto H, Akino M, et al. No positive association between adrenergic receptor variants of α_{2c}Del322-325, β_1Ser49, β_1Arg389 and the risk for heart failure in the Japanese population. Br J Clin Pharmacol 2005;60:414–7.
7. Small KM, Mialet-Perez J, Seman CA, Theiss CT, Brown KM, Liggett SB. Polymorphisms of cardiac presynaptic α_{2c} adrenergic receptors: diverse intragenic variability with haplotype-specific functional effects. Proc Natl Acad Sci U S A 2004;101:13020–5.

Letters to the Editor

Cost-Effectiveness of Upstream Versus Selective Glycoprotein IIb/IIIa Inhibitors for Acute Coronary Syndromes

As a result of extensive clinical research during the past decades, various treatment options are available today that might improve the prognosis of patients with coronary disease. One of the challenges for contemporary medicine is to implement these therapies rationally in clinical practice, in the appropriate patients at the appropriate time. In cost-conscious environments, treatment decisions should not only be based on the suspected benefit/harm ratio, but also on insights into therapy-related costs. Hence, pharmaco-economical analyses are becoming increasingly important in clinical cardiology.

In a recent issue of *JACC,* Glaser et al. (1) presented the results of a pharmaco-economical analysis in patients presenting with acute coronary syndromes (ACS) with moderate or high risk for cardiovascular events. They concluded that the strategy of routine upstream use of small-molecule (upstream-SM) glycoprotein (GP) IIb/IIIa inhibitors is a more cost-effective approach than the strategy of selective use of abciximab in patients who ultimately undergo percutaneous coronary intervention (PCI).

Glaser et al. (1) performed a decision-tree analysis and used data from clinical trials and a meta-analysis to define the probabilities on the decision nodes. However, several discrepancies exist between the applied probabilities and the data presented in the studies cited, most of which favor the upstream-SM strategy. As an example, Glaser assumes a relative risk (RR) in the range 0 (favoring upstream-SM) to 2.5 (favoring abciximab) for the incidence of death and myocardial infarction (MI) in the PCI setting; yet according to the TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcomes?) trial, in ACS patients the 95% confidence intervals (CIs) are 0.4 to 2.5 for death and 1.1 to 2.0 for MI (2). Interestingly, the RR of 0 implies that the upstream-SM strategy could produce survival for sure, which is unrealistic. Glaser assumes a RR of 1.0 for major bleeding complications in patients undergoing PCI, whereas the TARGET trial reports 1.0% major bleeds after upstream-SM versus 0.7% after abciximab (2). As a final example, Glaser et al. (1) assumes that the upstream-SM strategy, as compared to control therapy, is associated with a RR of 0.88 for death as well as for MI, with ranges varying from 0.41 to 0.47 to 0.95. In fact, the meta-analysis of the corresponding trials showed a 95% CI for the odds ratio of the composite end point of 0.82 to 0.95 (3).

If all variations between the assumptions of Glaser et al. (1) and the original studies are adjusted, results of the pharmaco-economical analysis are reversed: the selective abciximab strategy is then associated with a gain of 1,661 life-years per 100,000 patients, and avoids 173 major bleeds, as compared to upstream-SM. Still, this finding is unreliable. In fact, the presented decision-tree model was insufficiently adjusted for uncertainty because the sensitivity analysis that was applied did not alter all parameters at the same time. Monte-Carlo simulation demonstrates a tremendous uncertainty in any result of this study overall.

Decision-tree analyses might be useful to help clinicians make rational, consistent, and cost-conscious decisions. However, given the fact that average readers of clinical journals, including *JACC,* are not specialists in medical decision making and pharmaco-economics, authors of such analyses should be highly transparent in their choices, and they should emphasize the uncertainties of their conclusions. I am afraid that Glaser and colleagues missed opportunities in this respect.

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doi:10.1016/j.jacc.2006.10.020

REFERENCES

1. Glaser R, Glick HA, Herrmann HC, Kimmel SE. The role of risk stratification in the decision to provide upstream versus selective glycoprotein IIb/IIIa inhibitors for acute coronary syndromes: a cost-effectiveness analysis. J Am Coll Cardiol 2006;47:529–37.
2. Stone GW, Moliterno DJ, Bertrand M, et al. Impact of clinical syndrome acuity on the differential response to 2 glycoprotein IIb/IIIa inhibitors in patients undergoing coronary stenting: the TARGET trial. Circulation 2002;105:2347–54.
3. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359:189–98.